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14. ABSTRACT

In the first year of this proposal we have completed the human subjects authorization steps for both local (UCSF) and at the DOD human protection reviews and approvals. We have also implemented the Transcranial Magnetic Stimulation system for measuring central conduction times between brain and spinal cord and between spinal cord and muscles. The second stage of the project has begun for optimization of motor imaging protocol. Our initial work on test retest reliability has commenced and we have improved and optimized our spinal cord imaging as well as in partial development of fiber tracking techniques for segmentation of motor pathways in the brain, brainstem, and spinal cord. We have also acquired 7T MR spectroscopic imaging data for optimization and this data is currently being processed and evaluated. This work when completed will encompass the Aim 1 of the proposal. In aim 2, we propose to begin studies with the optimized protocol in MS patients. Our project timeline is between approximately 6 to 8 months delayed from the original SOW primarily due to delays in human subject authorization steps.

15. SUBJECT TERMS
Motor disability, spinal cord MRI, TMS, 7T MRI, MR spectroscopic imaging

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1. Introduction

The purpose of this project is to identify at a tissue level, the etiology of motor disability in MS patients. Motor disability is one of the primary disabling features of MS and is predictive of an aggressive progressive course of the disease. However, to date the associations between specific regional tissue injury and motor performance has been weak. These efforts have been particularly handicapped in part due to exclusion of complete imaging of the spinal cord in these studies. We have developed an efficient protocol for high quality imaging of the spinal cord. Utilizing state of the art structural and functional network changes from spinal cord and brain MRI, combined to neurophysiological measures of motor conduction, we propose to determine a stronger association between the neuronal injury and motor performance.

2. Keywords

Motor disability, spinal cord MRI, multiple sclerosis, transcranial magnetic stimulation, structural networks, functional networks, functional magnetic resonance imaging

3. Accomplishments

Specific Aim 1	Timeline	UCSF
Development of Quantitative Metrics of Motor Injury in Controls and Multiple Sclerosis	Months	
Local IRB Approval	1 - 2.5	Dr. Henry
Human Research Protection Review (DOD)	2.5 - 4	Dr. Henry
Develop reliable segmentation of motor neurons at the cortex and axons traversing the brain, brainstem and spinal cord	4 - 6	Dr. Henry

appropriate to MS patients.		
Develop reliable measures of motor neuron injury using quantitative MRI of the brain and spinal cord.	4 - 6	Dr. Henry
Develop reliable tissue based measures of motor neuron function and metabolic markers with MR spectroscopic imaging and functional MRI.	4 - 6	Dr. Henry
Milestone(s) Achieved: We will have defined an optimized protocol for acquisition of 3T and 7T MRI data to study of the structure and function of the motor system in MS.		
Specific Aim 2		
A Modeling of Motor injury and disability in Multiple Sclerosis		
Acquire MR markers of motor neuron injury, function, and loss and disease related metrics in MS patients at a baseline and 1-year follow-up time point.	6 - 24	Dr. Henry
Determine those variables that are correlated with motor function in a cross-sectional design.	12 - 24	Dr. Henry
Determine predictors of motor function change at 1-year follow-up.	18 - 24	Dr. Henry
Milestone(s) Achieved: (1) We would have specified and estimated a model of motor injury and disability in MS patients. (2) We would have specified and estimated a predictive model motor injury and disability in MS patients.		

a. <u>Major Goals of the Project</u>

The project is divided into 2 aims; Aim 1 proposed to complete local and DOD human subject approvals and development of an optimized MRI protocol. Aim 2 includes the studies in MS patients at baseline and 1 year follow-up. The milestones for Aim 1 are the completing of the human subjects approval and the development of the optimized MRI protocol.

b. <u>Accomplishments under these goals</u>

We have completed the human subjects approval process but have not been able to complete the first milestone due at this time primarily due to the much longer than expected time required to complete the human subjects authorization phases of this project. We are approximately 75% in completing Aim 1 to reach the first milestone — namely development of an optimized MRI protocol for the motor system. We anticipate completing this first milestone in the next 2 months.

Our accomplishments under these goals were:
- Local human subjects approval

- DOD human subjects approval
- Acquisition and implementation of the transcranial magnetic stimulation system required for time efficient application of our proposed technique. This step created a further delay in the project since the in-house stimulator needed to be upgraded due to age incompatibilities and therefore we needed to purchase a new coil for use in this project and implement on an alternate but similar stimulation platform in the same lab.
- Development of a high-resolution spinal cord imaging MRI protocol and test-retest experiments to evaluate reliability of estimating spinal cord grey and white matter segments. We have also developed a novel automated algorithm for delineation of spinal cord grey matter that has been validated on healthy subjects and now being tested on MS subjects.
- Development of an improved algorithm for development of a structural network template for the motor network. This algorithm uses recently developed clustering algorithm that enables automatic and objective methods for defining fiber tracts from diffusion MRI data. This template will now be tested as a method for constructing the structural motor networks in MS subjects.
- We have acquired scan-rescan MR spectroscopic imaging data on healthy controls at 7T and these data are now being processed and evaluated.
- We have acquired resting state fmri data on healthy controls and these data are currently being evaluated in terms of the relationship between motor and other resting state networks.

c. Opportunities for Training

Three bioengineering graduate students are doing the different methodological developments (spinal cord grey matter segmentation, function MRI motor networks, diffusion MRI structural networks) under the supervision of Dr. Henry. This project is currently also providing training for 2 young MS Neurologists (working on the transcranial magnetic stimulation, motor assessments, and relating to imaging metrics) who are acquiring neuroimaging skills from this project. These efforts constitute parts of the graduate thesis work for the graduate students and training for the neurologists towards academic research careers.

d. Dissemination to communities of interest

We have made abstracts to be submitted for conference presentations on the spinal cord segmentation and have a manuscript in preparation.

e. <u>Plans for the next reporting period</u>
We are approximately 6 to 8 months behind in the statement of work. In the next quarter we intend to complete aim 1 and reach the first milestone. To reach this end we need to acquire data on healthy controls with all the techniques currently developed for final optimization. Analyses will include final steps in defining structural and functional networks and integrating with spinal cord and TMS data. In this step we also need to define the appropriate motor clinical tasks.

Given the delayed statement of work, we anticipate needing an additional 3 quarters (9 months) extension on this project. In the second quarter of year 2, we will begin recruitment of MS patients and attempt to complete recruitment within this by the third quarter. Therefore, we will need approximately 3 more quarters to get the 1-year follow-up visits.

f. <u>Impact</u>
Even though in its early stages, this work may already provide substantive products. In particular, the automatic segmentation method is an important advancement in the ability to have objective accurate grey matter spinal cord areas and volumes.

g. <u>Changes/Problems</u>
There are no significant changes to the scope or implementation of the project. However the timeline needs to be extended by approximately 3 quarters (9 months) to ensure successful completion as proposed. The delays brought on by the human subjects approval process are concluded and we have progressed towards the first milestone as planned, albeit with a delayed timeline. We have developed higher-resolution spinal cord imaging that can be used in this project. In order to take advantage of the higher resolution higher quality spinal cord data, we need to program the pulse sequence. We propose to do this work to the benefit of the proposed project if it can be accomplished before MS patient recruitment begins. Our MR physicist who is funded on this project already may share effort with another MR physicist in our lab who has the specialized knowledge to do this pulse sequence programming.

h. <u>Participants</u>
There have been no changes in active participants funding and no other organizations involved.
Name: Roland Henry
Project Role: Principal Investigator
Effort in Months: 1.8 months
Contribution to the project: Dr. Henry is responsible for the overall design and implementation of the project as well as

supervision over all elements of data analyses and interpretation.
Funding Source: Dr. Henry is funded on this project as proposed.

Name: Stephen Hauser MD
Role: Co-Investigator, MS Clinician
Effort in Months: 0.6 months
Contribution to the project: Dr. Hauser provides clinical guidance and patient recruitment.
Funding Source: Dr. Hauser is funded on this project as proposed.

Name: Yan Li PhD
Role: Co-Investigator, Research Scientist
Effort in Months: 1.2 months
Contribution to the project: Dr Li's role is in the design, implementation, and analyses of 7T MR spectroscopic imaging data in the motor areas.
Funding Source: Dr. Li is funded on this project as proposed.

Name: Nico Papinutto PhD
Role: Co-Investigator, Research Scientist
Effort in Months: 0 months
Contribution to the project: Dr. Papinutto's role is in the design and implementation of advanced imaging in the spinal cord at 3T.
Funding Source: None used as yet since we have not programmed our new advanced sequence efficiently yet. Other funding for Dr. Papinutto comes from support of our 3T MRI Scanner recharge.

Name: Jung-Jiin Hsu PhD
Role: Research Scientist
Effort in Months: 0 months
Contribution to the project: Dr. Hsu has the specialized expertise to programme/implement on the Siemens software platform an time-wise efficient implementation of the high-resolution spinal cord imaging protocol developed by Dr. Papinutto.
Funding Source: None used as yet. Proposed 50% effort.

Name: Esha Datta
Role: Bioengineering Graduate Student
Effort in Months: No salary requested
Contribution to the project: Development of the Spinal Cord grey matter Segmentation algorithm and segmentation of cases
Funding Source: DOE Graduate Student Fellowship

Name: Kesshi Jordan
Role: Bioengineering Graduate Student

Effort in Months: No salary requested
Contribution to the project: Construction of template for structural motor networks from diffusion MRI data
Funding Source: DOE Graduate Student Fellowship

Name: Anisha Keshavan
Role: Bioengineering Graduate Student
Effort in Months: No salary requested
Contribution to the project: Development of methods to analyze functional MRI motor networks and relate to clinical metrics
Funding Source: Gift fund for MS research.

Name: Antje Bischof MD
Role: Postdoctoral Fellow, MS Neurologist
Effort in Months: No salary requested on project.
Contribution to the project: Implementation and execution of TMS on MS patients and healthy controls. Identification and segmentation of lesions in the motor network
Funding Sources: Swiss Fellowship, UCSF Department of Neurology gift fund for MS research.

Name: Regina Schlaeger MD
Role: Postdoctoral Fellow, MS Neurologist
Effort in Months: No salary used yet due to delays in project
Contribution to the project: Implementation and interpretation of TMS data. Created manual standard for spinal cord grey matter segmentation.
Funding Source: Dr. Schlaegers effort on this project is not yet utilized due to delays in the project aspects she will work on.

Name: Refujia O'Shea
Role: Clinical Coordinator
Effort in months: 0 Months
Contribution: The clinical coordinator will aid in scheduling and recruiting patients for scans and evaluations.
Funding source: No salary utilized yet due to delay in that aspect of the project.